

REMARKS

In view of the above amendment, Applicant believes the pending application is in condition for allowance. The numbered paragraphs below correspond to the numbered paragraphs in the Office Action.

Status of Claims

Claims 1-30 are pending. Claims 1, 3 and 24 have been amended herein to incorporate the changes suggested by the Examiner in the outstanding Office Action. Claims 17, 23 and 28-30 have been amended to correct the dependency. No new matter has been added by way of the present amendments to the claims.

1. Specification

In the outstanding Office Action, the Examiner has objected to the specification because of an informality in the first paragraph thereof. The first paragraph of the specification has been amended herein to state that U.S. Application No. 09/676,814 has matured into U.S. Patent 6,682,649. No new matter has been added by way of the present amendment to the specification. Reconsideration and withdrawal of this objection is respectfully requested.

2-8. 35 U.S.C. § 112, Second Paragraph

Claims 1-30 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse, and reconsideration and withdrawal of this rejection is respectfully requested.

The claims have been amended in order to address the antecedent basis issues raised by the Examiner in paragraphs 4, 5 and 6 of the Office Action.

With regard to paragraph 7 of the Office Action, Applicants have attached an annotated version of page 2 of the drawings to further explain the structure of the claims. Applicants submit that the annotated drawings clearly illustrate how the present claims

correspond to the specification and the drawings. The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*). See MPEP § 2163.02.

The assembly as claimed in Claim 3 describes a particular embodiment of the invention in which the claimed substrate is formed from two components, a first substrate component and a second substrate component which together make up the entire thickness of the substrate as a whole. This can be seen particularly in Figures 3a to 3d.

Accordingly, Applicants submit that the Examiner's concerns have been fully addressed. Reconsideration and withdrawal of the outstanding rejections are respectfully requested.

9-10. Rejections Under 35 U.S.C. § 103

It is confirmed that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

11-24. Rejection of Claims 1-15 and 17-30 Under 35 U.S.C. § 103

Claims 1-15 and 17-30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 99/31503 (hereinafter "WO '503") in view of Nisch et al. (U.S. Patent 6,31,940), Rubinsky et al. (U.S. Patent 6,300,108) or Kostyuk et al. (Nature, 257, pp. 691-693, October 1975).

Applicants respectfully traverse, and reconsideration and withdrawal of these rejections are respectfully requested.

WO 99/31503

The Examiner considers that WO '503 discloses an assembly having all the features of Claim 1 of the application apart from the feature that the assembly further comprises a plurality of flow channel structures created in the substrate for delivering liquid to said plurality of sites. The Examiner states that WO '503 suggests that the compartments of its substrate can be connected to conventional flow systems for delivering fluid to the various compartments. However, as recognized by the Examiner there is no mention nor suggestion in WO '503 of exactly how such flow systems would be connected to the substrate, nor is there any mention nor suggestion of using anything other than conventional flow systems.

The present invention is particularly directed towards a substrate and a method for determining and/or monitoring electrophysiological properties of ion channels of ion channel containing structures such as cells. The invention is particularly related to a substrate for patch clamp apparatus having high throughput and utilising only small amounts of test components, only small amounts of liquid carrier, and being capable of carrying out many tests in a short period of time by performing parallel tests on a number of cells simultaneously and independently.

When carrying out such tests it can be necessary to deliver liquid to the individual cells on which tests are being carried out in parallel.

An advantage of the present invention as claimed is that because the fluid may be delivered separately to each of the sites through flow channels that are created in the substrate, the size of assembly may be kept to a minimum, and bulky conventional flow structures are not required. In addition, through the formation of flow channel structures in the substrate, fluid can be accurately delivered to any particular site as required.

U.S. Patent 6,315,940 (Nisch)

An important feature of the assembly as claimed is that an ion channel containing structure may be positioned at a site by using an electrical field to generate an electroosmotic flow in a canal with an ionic solution containing the ion channel containing structure.

Nisch does not relate to the technical field of patch clamping (see for example column 2 lines 49 to 54).

An important feature of the Nisch disclosure is that the cell must be positioned accurately and centrally on the electrode. This is because electrical contact takes place in the Nisch apparatus only when there is physical contact between the cell and the electrode. (See for example column 1 lines 49 to 67, and column 2 lines 1 to 11).

There are numerous differences between the Nisch apparatus and that of the assembly as claimed. In particular, the electrodes 66, 67 are both in the same domain in a liquid biological environment 30. There is thus no way of measuring a current flowing between a reference electrode and a measuring electrode and passing through the ion channel containing structure.

A person skilled in the art of patch clamp techniques would not therefore combine the teachings of Nisch with the teachings of WO '503. Even if a skilled person were to make such combination, it can be seen from Nisch that the channel 23 identified by the Examiner is not a flow channel structure for delivering liquid to each of a plurality of sites. Instead, channel 23 is described as a common channel through which a negative pressure may be applied in order to cause cells 31 to be aspirated onto annular electrodes 21 (see particularly column 7 lines 18 to 20). The channels 23 therefore serve a very different purpose to the flow channels defined in Claim 1 of the present application particularly because they cannot be used to deliver liquid to a plurality of sites.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

US 6,300,108 (Rubinsky)

This patent is directed towards the fields of electroporation and a mass transfer across cell membranes (see column 1 lines 5 to 6). This is thus a different technology than that covered in the present application and also in the WO '503 document.

A particular embodiment described with reference to Figure 1 shows an example of a microdiffusion apparatus for a single biological cell for transporting material across the cell membrane without the application of an electric field.

A person skilled in the art of patch clamp techniques would not therefore consider combining the teachings of Rubinsky with those of WO '503. Even if the skilled person were motivated to make such combination, it is clear from the disclosure of Rubinsky that the channel 13, which is described as a portion carved out to define the lateral boundaries of the lower of the two liquid chambers, is not suitable for delivering liquid to a plurality of sites.

Kostyuk

The Kostyuk article again does not relate to patch clamping techniques. It would therefore not be obvious for a skilled person to combine the teachings of WO '503 with those of the Kostyuk article.

It is clear from Figure 1 of Kostyuk that the channel identified by the Examiner enables a negative pressure to be created below the cell in the lower compartment so that a suction effect is created in the pore. There is no mention nor suggestion anywhere in Kostyuk of a plurality of flow channel structures created in the substrate for delivering liquid to a plurality of sites.

Combination of Cited Prior Art

For the reasons set out hereinabove, the Applicants respectfully submit that the present invention as claimed in Claim 1 is novel and non-obvious in view of the prior art cited by the Examiner.

In accordance with *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007), in formulating a rejection under 35 USC 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

The Examiner bears the initial burden of presenting a prima facie case of obviousness. In *re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). “[R]ejections on

obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336, quoted with approval in KSR Int’l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007).

Applicants have submitted arguments above as to why the cited prior art references cannot be combined to arrive at the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Method Claims

For the reasons set out hereinabove with respect to Claim 1, Applicants submit that the method as claimed in Claim 24 of the application is novel and non-obvious in view of the prior art cited by the Examiner. Reconsideration and withdrawal of the outstanding rejection is respectfully requested.

Dependent Claims

In view of the foregoing arguments, since the invention as claimed in each of the independent claims of this application is novel and non-obvious, the dependent claims are also novel and non-obvious. Reconsideration and withdrawal of the outstanding rejection is respectfully requested.

25-26. Rejection of Claim 16 under 35 U.S.C. § 103

Claim 16 stands rejected as being unpatentable over WO ‘503 in view of any of Nisch, Rubinsky or Kostyuk and further in view of USP 5,393,401 to Knoll et al. (hereinafter “Knoll”). Applicants traverse.

The Examiner states that it would have been obvious to utilize the teaching of Knoll in the device of WO '503 in order to provide stable crystal surfaces along the etched out substrate well. However, the Examiner has not provided any scientific basis for reaching this conclusion.

“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336, quoted with approval in KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007).

Moreover, Applicants respectfully submit that the Examiner is engaging in impermissible hindsight reasoning to reject the present claim. Knoll merely mentions the angle of 54.75 of the surfaces, without teaching of any benefit derived from using this particular configuration in the microwell. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

28-29. Rejection of Claims 1-3 on the Ground of Obviousness-Type Double Patenting

The Examiner's rejection on the grounds of obviousness-type double-patenting heading over the claims of granted US Patent No. 6,682,649 appears to be based on the proposition that the feature of having flow channels formed in the substrate is obvious in view of the prior art cited by the Examiner. Applicants respectfully traverse.

This issue is addressed in the arguments set forth above. Therefore, because the claimed invention is patentable in view of the prior art cited above, the double patenting rejection should be overcome. Reconsideration and withdrawal of the outstanding rejection is respectfully requested.

In view of the foregoing, it is believed that claims are allowable. A Notice of Allowance is earnestly solicited.

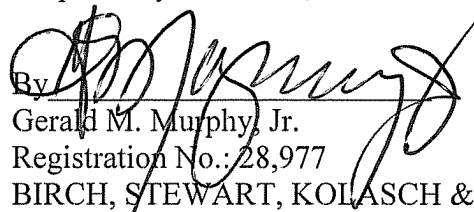
Conclusion

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Monique T. Cole, Reg.. No. 60,154 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for a

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Respectfully submitted,

By 

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Attachment: Annotated Sheet 2/4 of Drawing Figures